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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,162	05/31/2001	Isaiah J. Fidler	UTSC:643US/SLH	8776

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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 02/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/872,162	FIDLER ET AL.
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 January 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-194 is/are pending in the application.
- 4a) Of the above claim(s) 1-132, 136 and 143-194 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 133-135 and 137-142 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6 and 7</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-194 are pending in the present application.

Applicant's election without traverse of Group IV (claims 133-144) in Paper No. 10 is acknowledged. Applicant further elected the following species: (a) IFN β as a species of immunomodulator; and (b) an exogenous construct encoding an immunomodulator as a species of an exogenous construct.

Accordingly, claims 1-132, 136 and 143-194 are withdrawn from further consideration because they are drawn to non-elected inventions and non-elected species.

Claims 133-135 and 137-142 are examined on the merits herein.

Information Disclosure Statement

The Japanese reference (B1) listed in the PTO-1449 form filed on 9/28/01 in Paper No. 6 has not been considered by Examiner because the reference is in Japanese. Should Applicants wish Examiner to consider this document, a translated version is required.

Claim Objections

Claims 134 and 139-141 are objected to because they contain non-elected species of an immunomodulator (species other than the elected IFN- β).

Claim Rejections - 35 USC § 112

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 133-135 and 137-142 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method of inhibiting cancer growth in a host having a cancer, said method comprising:

- a) isolating cancer cells from the host;
- b) rendering said cancer cells inactive;
- c) reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell composition comprising insect cells containing a recombinant baculovirus vector encoding a β -interferon wherein said β -interferon is expressed in the insect cells; does not reasonably provide enablement for a method of treating cancer in a host utilizing inactivated cancer cells and any insect cell composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

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Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention and species, the claims are drawn to a method of treating cancer comprising: (a) isolating cancer cells from a host; (b) rendering said cancer cells inactive; (c) reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell composition; the same method wherein said insect cell composition further comprising IFN β .

The specification teaches by exemplification showing that upon subcutaneous inoculation of C57BL6 mice with irradiated B16BL6 tumor cells alone or with lyophilized H5IFN β (H5 insect cells infected with a recombinant baculovirus expressing IFN β) or with H5BV (control H5 insect cells), followed by a subsequent challenge with viable B16BL6 tumor cells, there is a statistically significant reduction in challenge tumor growth with a mixture of irradiated B16BL6 and lyophilized H5 insect cells infected with IFN β (see example 13 and Fig. 23). The specification further discloses that there is also a significant difference in observed tumor volume between mice injected intratumorally with a combination of IFN β and an insect cell composition and mice injected with either IFN β alone or saline alone (see example 14 and Fig. 24).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(a) The breadth of the claims. The broad claims 133 and 137-140 encompass a method of treating cancer in a host using any insect cell composition in conjunction with inactivated cancer cells obtained from the same host in the absence of any form of IFN β . With respect to claims 134-136, IFN β is not necessarily provided in the form of an insect cell composition genetically modified to express the IFN β , and that such IFN β is introduced into the host by any route of administration (including a systemic delivery) for cancer treatment.

(b) The amount of direction or guidance provided. Apart from the exemplification related to the elected invention as shown in Examples 13 and 14 discussed above, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a broad range of therapeutic effects encompassed within the scope of treating a cancer in a host (e.g., inhibiting, eradicating as well as preventing the reoccurrence of cancer) using inactivated cancer cells obtained from the host and any insect cell composition. It is not clear that any insect cell would function as an effective adjuvant for the co-administered inactivated cancer cells to yield the broad therapeutic effects contemplated by Applicants. Even with the utilization of lyophilized H5 insect cells infected with a recombinant baculovirus expressing IFN β in combination with irradiated B16BL6 tumor cells, tumor growth was still observed upon challenge of the vaccinated mice with viable B16BL6 tumor cells, although the challenge tumor growth is statistically significantly reduced (see Fig. 23), let alone for any insect cell composition as encompassed by the breadth of the claims. Applicants also show that there is no statistically significant reduction in challenge tumor growth for

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the mixture of irradiated B16BL6 and H5BV cells or H5 cells (control insect cells) in comparison with the challenge tumor growth in naïve mice or in mice pretreated with irradiated B16BL6 alone (see Fig. 23). Furthermore, intratumoral injection of IFN β alone or in combination with an insect cell composition does not eradicate the treated cancer because tumor growth is still observed (see Fig. 24). Additionally, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain the contemplated therapeutic effects by introducing IFN β into a treated host by any route of administration, and wherein the IFN β is not expressed by recombinant insect cells. Particularly, Xie et al. (Clin. Cancer Res. 3:2283-2294, 1997; IDS) already teach that pharmacokinetic studies have demonstrated that the half-life of IFNs in the circulation of patients is in order of minutes, and that the lack of sustained levels of administered IFNs may have been responsible for the failure to inhibit or eradicate tumors (page 2283, col. 2, second full paragraph). Since the prior art at the effective filing date of the present application does not provide such guidance on the aforementioned issues, it is incumbent upon the present application to do so. With the lack of sufficient guidance provided by this disclosure, it would still have required undue experimentation for a skilled artisan to make and use the methods as broadly claimed.

(c) The state of the prior art and the unpredictability of the prior art. At the effective filing date of the present application, the attainment of the full scope of cancer therapeutic effects contemplated by Applicants for the methods as claimed is neither routine nor predictable. Moreover, it should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). Additionally, Xie et al. already note the

obstacles or difficulties known in the art for achieving a sustained and effective level of IFNs (not in the form of a recombinant insect cell expressing IFNs) in circulation of patients to inhibit or eradicate tumors. Given the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, the unpredictability of the physiological art in general, especially for attaining therapeutic effects in cancer treatment, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 135 and 138-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 135 recite the limitation "said immunomodulator is IFN β " in line 1 of claim 135. There is insufficient antecedent basis for this limitation in the claim. This is because in the method of claim 133 from which claim 135 is dependent upon, there is no recitation of any immunomodulator. The metes and bounds of the claim are not clearly determined.

In claim 138, the phrase “wherein said cancer is diffuse” is unclear. Does the term “diffuse” refer to a morphological description of the cancer? Or does it refer to the spreading or metastasis of the cancer? The metes and bounds of the claims are not clearly determined.

Claim 139 and its dependent claims recite the limitation “said exogenous DNA” in line 1 of claim 139. There is insufficient antecedent basis for this limitation in the claim. This is because in the method of claim 133 from which claim 139 is dependent upon, there is no recitation of any exogenous DNA. Thus, there is no explicit linkage between the pharmaceutical composition of claim 133 and the DNA of claim 139. The metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 133-135 and 137-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al. (U.S. 5,689,562) in view of Dong et al. (Cancer Research 59:872-879, 1999; IDS), Smith et al. (U.S. 6,224,882) and Smith et al. (4,745,051; IDS).

With respect to the elected invention, the claims are drawn to a method of treating cancer comprising: (a) isolating cancer cells from a host; (b) rendering said cancer cells inactive; (c) reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell composition; the same method wherein said insect cell composition further comprising IFN β .

With respect to the enabled scope of the present invention and the elected invention, Sobol et al. teach a method for inhibiting the growth of tumor cells in a patient comprising the stimulation of that patient's immune response against the tumor cells by administering to said patient a composition comprising tumor antigens and cytokine expressing cells genetically modified to express a cytokine gene product, wherein said cytokine-expressing cells are not tumor cells (see Summary of the Invention, cols. 2-3; and the claims). Exemplified cytokine genes to be expressed in the method of Sobol et al. include the genes for IL-2, gamma-interferon (c-INF) and other cytokines readily available in the art (col. 5, lines 48-50). Sobol et al. teach that apart from IL-2, other cytokines such as IL-4, alpha interferon (α -INF) and gamma interferon (c-INF) have been used to stimulate immune responses to tumor cells (col. 1, lines 43-46). Sobol et

al. further teach that when viable tumor cells are utilized in immunizations as a source of tumor antigens, the tumor cells can be inactivated so that they do not grow in the patient, and inactivation can be accomplished by several methods such as irradiation prior to immunization (col. 7, lines 29-36). Tumor cells bearing tumor-associated antigens are isolated from the patient (col. 6, lines 61-62). Additionally, Sobol et al. teach that autologous and non-autologous cells can be selected and processed to generate cytokine expressing cells (col. 5, lines 33-44).

Sobol et al. do not specifically teach a method of reintroducing inactivated cancer cells in a pharmaceutical composition further comprising an insect cell composition comprising IFN β to stimulate a systemic active immune response in a patient in need thereof to inhibit the growth of said cancer cells.

However, at the effective filing date of the present application, Smith et al. (U.S. 6,224,882) already teach that insect cells from the Lepidopteran species or insect cells subject to baculovirus infection and their fractions can be utilized as an adjuvant for immunogenic, immunological, antigenic or vaccine compositions (see abstract and Summary of the Invention). Smith et al. (U.S. 6,224,882) further teach that the insect cells can be infected with a recombinant baculovirus expressing an epitope of interest or antigen.

Smith et al. (U.S. 4,745,051) also already teach that insect cells subject to recombinant baculovirus infection are capable of expressing any selected desired gene products, including the human IFN β gene product that can be synthesized and efficiently secreted from the host insect cells (see Summary of the invention).

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Dong et al. teach that it has been known in the art that IFNs can be efficacious against many hematopoietic neoplasms and some vascular tumors (page 872, col. 2, second full paragraph). Dong et al. further teach that IFN β can inhibit tumor growth and metastasis of human prostate cancer cells by suppression of tumor angiogenesis and activation of tumoricidal host effector cells (see abstract). Furthermore, Dong et al. teach that IFN β has been shown to be more potent than IFN- α at least in inhibiting for the proliferation of human prostate cancer cells (page 872, col. 2, second full paragraph).

Accordingly, at the effective filing date of the present application it would have been obvious and within the level of skill for an ordinary skilled artisan to modify the method of Sobol et al. by utilizing insect cells infected with recombinant baculovirus expressing IFN β as a source of cytokine expressing cells, for the stimulation of a systemic active immune response in a patient in need thereof to inhibit the growth of cancer cells in light of the teachings of Smith et al. (U.S. 6,224,882), Smith et al. (4,745,051) and Dong et al. as discussed above.

One of ordinary skilled artisan would have been motivated to carry out the above modification because insects cells whether genetically modified with a recombinant baculovirus expressing IFN- β or not, can function as an adjuvant for the co-administered inactivated tumor cells to stimulate a systemic active immune response specific to said tumor cells in a patient. Additionally, since IFN β has been shown to be efficacious against many hematopoietic neoplasms, some vascular tumors as well as human prostate cancer, and its effects are mediated through the suppression of tumor

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angiogenesis and activation of tumoricidal host effector cells as taught by Dong et al., one of ordinary skilled artisan would have been further motivated to utilize insects cells infected with a recombinant baculovirus expressing IFN β , especially IFN β has been taught to be more potent than IFN- α at least in inhibiting for the proliferation of human prostate cancer cells by Dong et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

Gerald G. Leffers Jr.
PATENT EXAMINER
Gerald G. Leffers Jr.
A.4.1636